

## Probing sporadic and familial Alzheimer's disease using induced pluripotent stem cells.

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### Public Summary:

Human induced pluripotent stem cells from patients carrying disease-causing mutations can be studied in cell culture to reveal characteristics of the disease that cannot be determined from mouse models of the disease. In this case, Alzheimer's disease was studied by analysis of iPSCs derived from people carrying familial mutations that cause the disease.

### Scientific Abstract:

Our understanding of Alzheimer's disease pathogenesis is currently limited by difficulties in obtaining live neurons from patients and the inability to model the sporadic form of the disease. It may be possible to overcome these challenges by reprogramming primary cells from patients into induced pluripotent stem cells (iPSCs). Here we reprogrammed primary fibroblasts from two patients with familial Alzheimer's disease, both caused by a duplication of the amyloid-beta precursor protein gene (APP; termed APP(Dp)), two with sporadic Alzheimer's disease (termed sAD1, sAD2) and two non-demented control individuals into iPSC lines. Neurons from differentiated cultures were purified with fluorescence-activated cell sorting and characterized. Purified cultures contained more than 90% neurons, clustered with fetal brain messenger RNA samples by microarray criteria, and could form functional synaptic contacts. Virtually all cells exhibited normal electrophysiological activity. Relative to controls, iPSC-derived, purified neurons from the two APP(Dp) patients and patient sAD2 exhibited significantly higher levels of the pathological markers amyloid-beta(1-40), phospho-tau(Thr 231) and active glycogen synthase kinase-3beta (aGSK-3beta). Neurons from APP(Dp) and sAD2 patients also accumulated large RAB5-positive early endosomes compared to controls. Treatment of purified neurons with beta-secretase inhibitors, but not gamma-secretase inhibitors, caused significant reductions in phospho-Tau(Thr 231) and aGSK-3beta levels. These results suggest a direct relationship between APP proteolytic processing, but not amyloid-beta, in GSK-3beta activation and tau phosphorylation in human neurons. Additionally, we observed that neurons with the genome of one sAD patient exhibited the phenotypes seen in familial Alzheimer's disease samples. More generally, we demonstrate that iPSC technology can be used to observe phenotypes relevant to Alzheimer's disease, even though it can take decades for overt disease to manifest in patients.

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